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# Comparison of primary plexogenic arteriopathy in adults and children
## *A morphometric study in 40 patients*

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SUMMARY Pulmonary vascular changes were studied in histological sections from 15 children and 25 adults with primary plexogenic arteriopathy. The severity of medial hypertrophy and degree of vasoconstriction were measured in histological sections and there was a close correlation between these two variables in both children and adults. More advanced arterial changes, expressed as an index of pulmonary vascular disease, were more common in adults, and their severity correlated positively with the degree of medial hypertrophy. No such correlation was found in children. There were similar numbers of plexiform lesions per square centimetre in children and adults, so that the differences in the indices of pulmonary vascular disease were mainly due to the intimal changes. Concentric laminar intimal fibrosis was more severe in adults. It is suggested that intensive spastic vasoconstriction results in the development of fibrinoid necrosis and subsequently of plexiform lesions and that this may happen irrespective of the presence of severe intimal fibrosis. This suggests that children with primary plexogenic arteriopathy in whom plexiform lesions have not yet developed are more likely to respond to vasodilator treatment than are adults in whom irreversible changes associated with intimal fibrosis have developed.

The vasoconstrictive form of primary pulmonary hypertension, associated with primary plexogenic pulmonary arteriopathy, is an uncommon disease that predominantly affects children and young or middle aged adults. Pulmonary vascular lesions in this condition differ morphologically from those in other forms of unexplained pulmonary hypertension such as pulmonary veno-occlusive disease or silent recurrent thromboembolism. The clinical picture, however, is often indistinguishable and a lung biopsy may be necessary for an accurate diagnosis. So far, various therapeutic approaches have met with limited success, although vasodilator treatment may be effective in some cases.

There are differences between adults and children with primary pulmonary hypertension. Adult women are more commonly affected than men, whereas in children the sexes are equally affected. Also it was our impression that there were differences in the development of the various arterial lesions. To determine the extent of these differences we have studied the pulmonary arteries in tissue from 15 children and 25 adults with primary plexogenic arteriopathy.

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### Patients and methods

At least five histological sections of lung tissue obtained at necropsy were available from each of 40 patients; 15 were aged from 1 month to 12 years (four male and 11 female) and 25 were aged from 16 to 64 years (six male and 19 female) (Table). All died of severe pulmonary hypertension. The duration of illness was known to us in 34 cases. We also examined lung tissue from a control group of 34 individuals (aged from newborn to 33 years) without heart or lung disease.

Table *Clinical and morphological data in 40 patients with primary pulmonary hypertension*

| | Case | Age (yr) | Sex | Duration of illness (yr) | No of pulmonary arteries which scored | | | | IPVD | No of plexiform lesions (per cm²) | Thrombus | Medial thickness ($D_R$ = 100 μm) | Degree of vasoconstrictio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1 | 2 | 3 | 4 | | | | | |
| Children: | | | | | | | | | | | | | |
| | 1 | 0·1 | M | 0·1 | 100 | 0 | 3 | 0 | 1·1 | 0 | – | 19·6 | 2·8 |
| | 2 | 1 | F | 0·8 | 39 | 1 | 30 | 10 | 2·1 | 0·4 | – | 14·1 | 1·8 |
| | 3 | 1 | M | Unknown | 67 | 0 | 56 | 6 | 2·0 | 0·8 | – | 17·7 | 2·9 |
| | 4 | 1·3 | F | Unknown | 13 | 0 | 21 | 9 | 2·6 | 1·6 | – | 13·2 | 2·3 |
| | 5 | 2·5 | M | 0·5 | 100 | 0 | 4 | 0 | 1·1 | 0 | + | 17·6 | 2·3 |
| | 6 | 3 | F | Unknown | 83 | 2 | 17 | 0 | 1·4 | 0 | – | 14·9 | 2·3 |
| | 7 | 4 | F | 1 | 32 | 6 | 27 | 12 | 2·3 | 0·8 | – | 12·3 | 2·3 |
| | 8 | 5·5 | F | Unknown | 12 | 0 | 52 | 29 | 3·1 | 2·5 | – | 17·1 | 2·2 |
| | 9 | 6 | F | 1 | 13 | 0 | 48 | 11 | 2·8 | 4·2 | – | 17·1 | 2·3 |
| | 10 | 6 | F | 0·2 | 6 | 2 | 6 | 20 | 3·2 | 1·7 | – | 19·3 | 3·3 |
| | 11 | 9 | M | 1 | 9 | 1 | 21 | 12 | 2·8 | 0 | – | 11·7 | 2·3 |
| | 12 | 10 | F | Unknown | 35 | 1 | 30 | 3 | 2·0 | 0 | – | 11·2 | 1·8 |
| | 13 | 11 | F | 4·5 | 48 | 0 | 17 | 2 | 1·6 | 0 | – | 12·2 | 1·8 |
| | 14 | 11 | F | Unknown | 13 | 0 | 20 | 12 | 2·7 | 0·5 | – | 12·1 | 2·4 |
| | 15 | 12 | F | 2 | 37 | 14 | 41 | 0 | 2·0 | 0 | – | 13·5 | 2·7 |
| Adults: | | | | | | | | | | | | | |
| | 16 | 16 | M | 3 | 12 | 0 | 20 | 21 | 2·9 | 0 | – | 25·7 | 3·0 |
| | 17 | 16 | M | 3 | 23 | 0 | 18 | 36 | 2·9 | 0 | – | 16·7 | 2·0 |
| | 18 | 16 | F | 3 | 15 | 0 | 47 | 34 | 3·0 | 0·9 | – | 20·5 | 2·0 |
| | 19 | 17 | F | 6 | 0 | 0 | 61 | 34 | 3·4 | 0·5 | ++ | 12·2 | 2·0 |
| | 20 | 18 | M | 1·5 | 2 | 0 | 36 | 30 | 3·4 | 0 | + | 24·8 | 3·8 |
| | 21 | 19 | F | 3 | 42 | 6 | 77 | 20 | 2·5 | 2·4 | – | 15·9 | 2·7 |
| | 22 | 23 | M | 5 | 2 | 0 | 20 | 26 | 3·5 | 0·2 | – | 14·3 | 2·9 |
| | 23 | 26 | F | 6 | 7 | 0 | 40 | 18 | 3·1 | 2·9 | – | 16·4 | 2·1 |
| | 24 | 27 | F | 2 | 30 | 1 | 19 | 2 | 1·9 | 0 | – | 4·7 | 1·4 |
| | 25 | 28 | F | 2 | 0 | 0 | 32 | 38 | 3·5 | 0·7 | ++ | 16·0 | 2·3 |
| | 26 | 29 | F | 11 | 3 | 0 | 28 | 48 | 3·1 | 0·4 | – | 12·5 | 1·7 |
| | 27 | 29 | F | 4 | 38 | 0 | 34 | 0 | 1·9 | 0 | – | 10·6 | 2·8 |
| | 28 | 30 | F | 3 | 7 | 0 | 9 | 22 | 3·2 | 0 | – | 28·1 | 3·1 |
| | 29 | 31 | F | 5 | 0 | 0 | 24 | 24 | 3·5 | 0 | ++ | 19·2 | 2·1 |
| | 30 | 31 | F | 11 | 49 | 0 | 53 | 17 | 2·3 | 0·1 | – | 13·3 | 2·0 |
| | 31 | 32 | F | 2 | 25 | 0 | 29 | 47 | 3·0 | 0·4 | – | 17·7 | 3·2 |
| | 32 | 35 | F | 5 | 22 | 2 | 63 | 22 | 2·8 | 0·5 | – | 10·9 | 1·9 |
| | 33 | 35 | F | 4 | 19 | 0 | 64 | 24 | 2·9 | 1·8 | – | 8·6 | 2·2 |
| | 34 | 40 | M | 1·5 | 5 | 0 | 19 | 12 | 3·1 | 0·5 | ++ | 18·6 | 3·0 |
| | 35 | 41 | F | 3 | 4 | 0 | 21 | 16 | 3·2 | 0·6 | ++ | 16·1 | 1·9 |
| | 36 | 42 | F | 1·5 | 5 | 0 | 19 | 12 | 3·1 | 0·5 | + | 18·6 | 3·0 |
| | 37 | 50 | F | 3 | 0 | 0 | 26 | 15 | 3·4 | 1·2 | + | 8·3 | 1·6 |
| | 38 | 51 | F | 2 | 6 | 0 | 21 | 30 | 3·3 | 0·4 | + | 8·6 | 2·3 |
| | 39 | 62 | F | 3 | 8 | 0 | 35 | 23 | 3·1 | 0 | – | 24·4 | 2·7 |
| | 40 | 64 | M | 7 | 1 | 0 | 36 | 37 | 3·5 | 2·6 | – | 20·6 | 2·0 |

$D_R$ = 100 μm represents the thickness of the media at a pulmonary arterial radius of 100 μm. IPVD, index of pulmonary vascular disease.

Histological sections were stained routinely with haematoxylin and eosin and with van Gieson's stain. We measured the thickness of the media by a method previously reported.[1] We assumed that the degree of vasoconstriction of pulmonary arteries is proportional to the ratio between medial thickness in a state of postmortem contraction and that after complete expansion of the internal elastic lamina.

In each case about 20 pulmonary arteries with an approximately circular cross section were traced on to paper. The radius (R') and the medial thickness on opposite sides of the vessel in its contracted state ($D_1$, $D_2$) were measured and the average medial thickness (D') and the ratio D':R' calculated (Fig 1). The medial thickness (D) and radius (R) of the artery in the hypothetical expanded state from the length of the internal elastic lamina and surface area

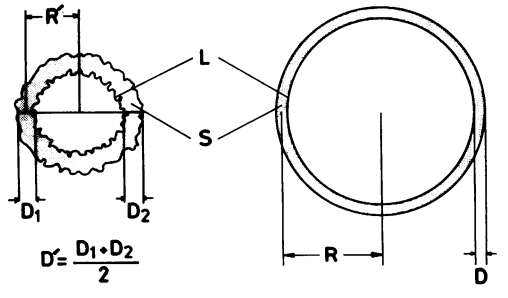


Fig. 1 *Morphometric assessment of medial thickness and degree of vasoconstriction. Schematic representation of artery in contracted (left) and hypothetically expanded state (right). R, radius, D, medial thickness, L length of internal elastic lamina, S, surface area of media.*

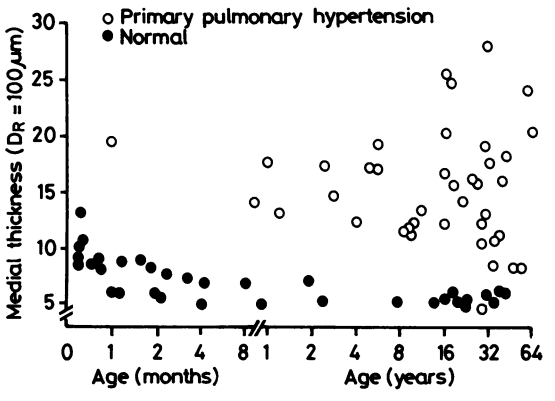


Fig. 2 *Medial thickness of pulmonary arteries (when pulmonary arterial radius is 100 μm) plotted against age in patients with primary pulmonary hypertension and in normal controls.*

of the media were calculated. A measure of the degree of vasoconstriction can then be calculated by the formula D′/R′ ÷ D/R. To exclude the effects of secondary medial atrophy caused by intimal fibrosis and of excessive dilatation, we made no measurements of arteries with severe intimal fibrosis or with dilatation lesions.

We also assessed the severity of the more advanced vascular lesions by means of a semi-quantitative index of pulmonary vascular disease.[2] This index is based on a score ranging from 1 to 4: 1, no intimal lesions; 2, cellular proliferation; 3, fibrous and fibroelastic intimal proliferation; 4, partial or total destruction of media, as in fibrinoid necrosis, dilatation lesions, and plexiform lesions. A score was given to each pulmonary artery in our sections and the index of pulmonary vascular disease was calculated as the mean score of all arteries examined in an individual case. We did not attempt to distinguish between the various types of intimal fibrosis. Therefore, post-thrombotic and postembolic intimal fibrosis have been included in the score, although most intimal lesions were of the concentric laminar type. This may to some extent influence the score of those patients who had complicating thromboembolism. Plexiform lesions were counted in the sections and, after we had established the surface area of the sections by planimetry, their number per square centimetre of histological section was calculated.

The number of pulmonary arteries scoring 1, 2, 3, or 4, the index of pulmonary vascular disease, the number of plexiform lesions, the presence of thrombus, the medial thickness ($D_R$ = 100 μm), and the degree of vasoconstriction are shown in the Table for children and for adults. $D_R$ = 100 μm represents the thickness of the media at a pulmonary arterial radius of 100 μm.

Student's *t* test was used to assess the statistical significance of differences between groups. The correlation between index of pulmonary vascular disease and other variables was tested by the Mann-Whitney U test because the index score was essentially non-parametric.

## Results

### PULMONARY ARTERIAL MEDIAL THICKNESS AND VASOCONSTRICTION

Figure 2 shows the relation between age and medial thickness of pulmonary arteries in patients with primary pulmonary hypertension and in controls. In the controls medial thickness at birth was approximately 10 μm but after the age of 5 months it was consistently 5–7 μm. Although medial thickness var-

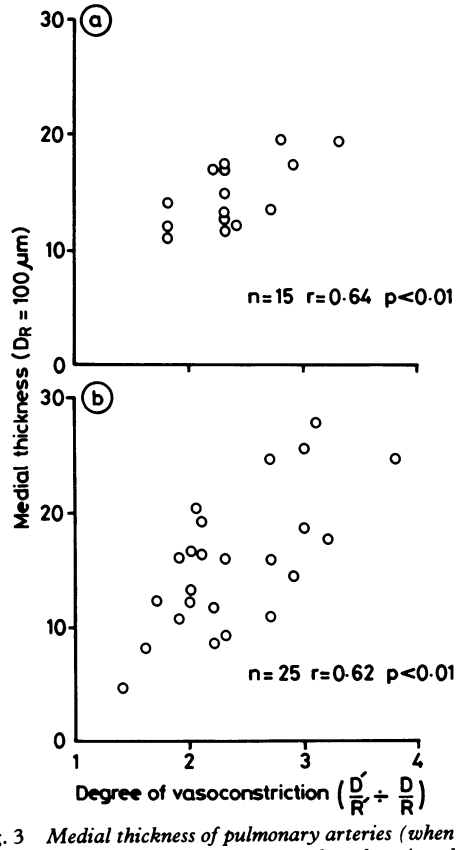


Fig. 3 *Medial thickness of pulmonary arteries (when pulmonary arterial radius is 100 μm) plotted against degree of vasoconstriction in 15 children (a) and 25 adults (b) with primary pulmonary hypertension. In both groups there is a significant positive correlation.*

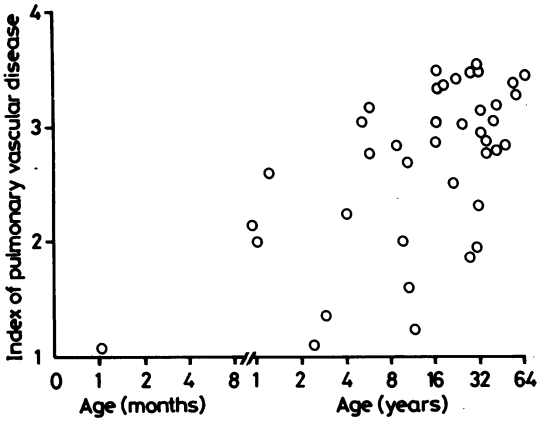


Fig. 4 *Index of pulmonary vascular disease plotted against age in patients with primary pulmonary hypertension.*

ied considerably in patients with primary pulmonary hypertension, it was generally much thicker than in the controls. In children with primary pulmonary hypertension medial thickness ranged from 11·2 to 19·6 μm (mean (SD) 14·9(2·9) μm), while in adults it ranged from 4·7 to 28·1 μm (mean 15·1(6·7) μm). The difference between adults and children is not statistically significant. The presence or absence of thromboemboli had no apparent influence on medial thickness. There was a statistically significant ($p < 0·01$) correlation between medial thickness and degree of vasoconstriction in children and in adults with primary pulmonary hypertension (Fig. 3).

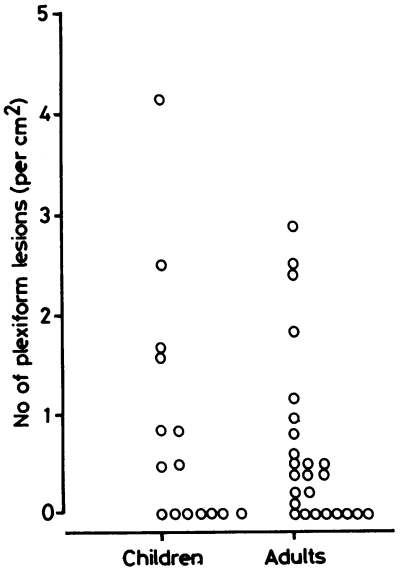


Fig. 5 *A comparison of the number of plexiform lesions in children and in adults with primary pulmonary hypertension.*

ADVANCED PULMONARY ARTERIAL CHANGES

The index of pulmonary vascular disease varied from 1·1 to 3·5 (mean 2·5). In 24 of the 40 cases there was no cellular intimal proliferation (score 2). On the other hand more severe changes (scores 3 and 4) were seen in most cases. The index of pulmonary vascular disease tended to increase with age, although there was some variation (Fig. 4). In children scores ranged from 1·1 to 3·2 (mean 2·2) while in adults scores ranged from 1·9 to 3·5 (mean 3·0) ($p < 0·001$). There were plexiform lesions in eight of 15 children and in 17 of 25 adults. They varied from scarce to numerous (maximum 4·2/cm²). Numbers of plexiform lesions per square centimetre in adults and children were not significantly different (Fig. 5).

In children with primary pulmonary hypertension there was no correlation between medial thickness

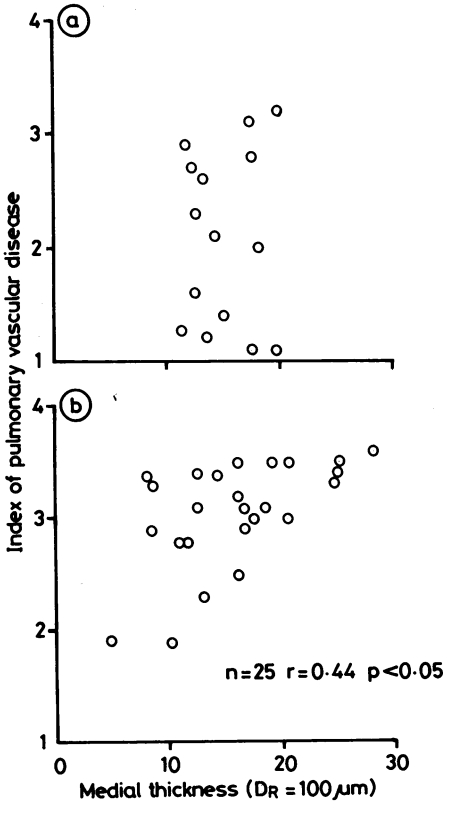


Fig. 6 *Index of pulmonary vascular disease plotted against medial thickness in 15 children (a) and 25 adults (b) with primary pulmonary hypertension. There is a positive correlation in adults but not in children.*

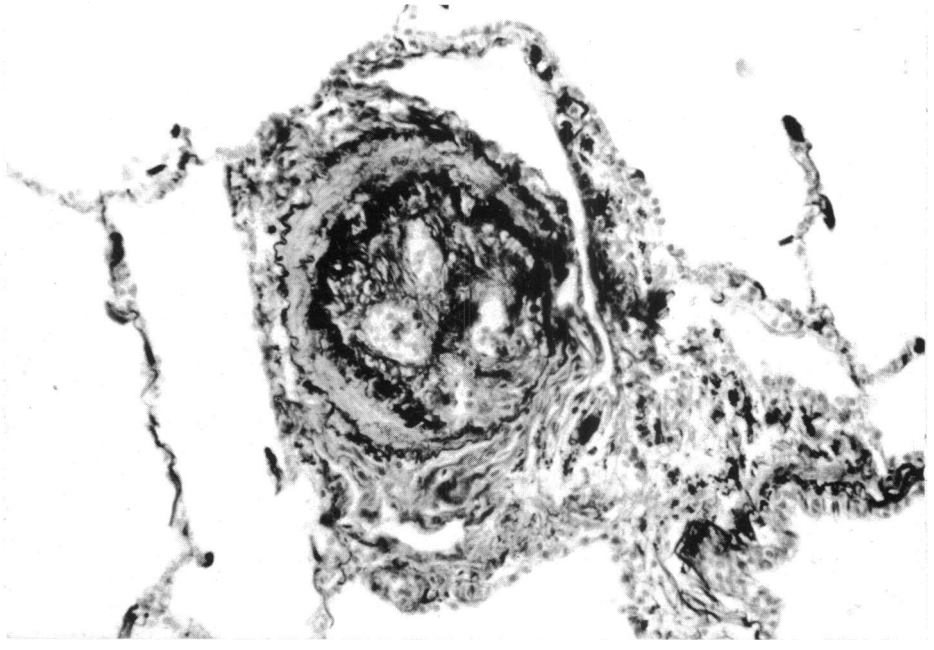

Fig. 7 *Muscular pulmonary artery with intravascular fibrous septa in a patient with primary pulmonary hypertension (case 35). van Geison's stain ( × 200) (original magnification).*

and index of pulmonary vascular disease but medial thickness in children was found within a narrow range (Fig. 6a). In adults medial thickness varied more and there was a positive and significant ($p < 0.05$) correlation between the two variables (Fig. 6b).

THROMBOTIC LESIONS

In ten of the 40 patients with plexogenic arteriopathy sections also showed thrombotic or thromboembolic lesions. These were frequent in five (cases 19, 25, 29, 34, and 35). These lesions appeared as eccentric patches of intimal fibrosis or as intravascular fibrous septa (Fig. 7).

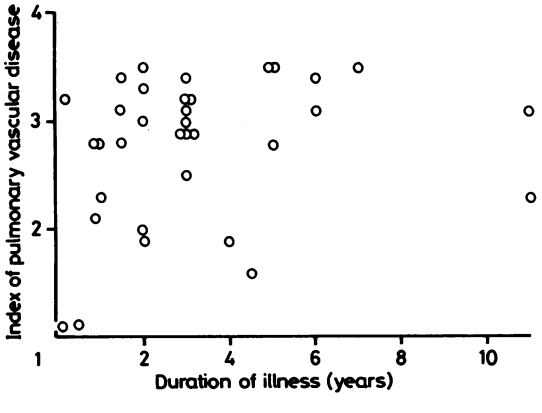


Fig. 8 *Index of pulmonary vascular disease plotted against duration of illness in patients with primary pulmonary hypertension.*

DURATION OF ILLNESS

The duration of illness was known in 34 patients. There was no correlation with the index of pulmonary vascular disease (Fig. 8). The duration of illness, however, was shorter in children than in adults. Of 13 patients in whom symptoms first developed in childhood, seven had been ill for less that two years and six for two years or more; in 21 patients in whom symptoms first developed in adult life the corresponding numbers of patients were three and 18.

## Discussion

The pattern of pulmonary vascular lesions in primary pulmonary hypertension resembles that seen in congenital heart disease with a left to right shunt—medial hypertrophy, cellular intimal proliferation, and concentric laminar intimal fibrosis, followed by fibrinoid necrosis, dilatation lesions, and plexiform lesions. Since the vascular changes tend to develop in this order, the advanced lesions may be absent in earlier stages, particularly in children, when there may be medial hypertrophy only.

The causes of primary pulmonary hypertension are unknown but it has been suggested that the initial event is an intense spastic vasoconstriction.[3] In two large series there were three to four times as many women as men, whereas the sexes were equally affected in children.[3 4] In the present smaller series, if those adults in whom the disease developed before the age of 16 years are included with the children, the ratios of females to males are 4·2: and 2·2 for adults and children.

Like Walcott *et al*[4] we found no correlation between the severity of pulmonary vascular disease and duration of illness. Like Evans *et al*[5] we observed a shorter duration of illness in children than in adults. Early right ventricular failure and death may occur in children in the absence of advanced vascular lesions.

Our method of assessment made it possible to compare the degrees of medial hypertrophy and vasoconstriction, although the contribution of postmortem contraction to vasoconstriction could not be assessed. We know from experimental studies that active constriction of pulmonary arteries during life can be seen in histological sections after death.[6] We therefore assume that our method gives a reliable estimate of the degree of vasoconstriction. We found medial hypertrophy was consistently present in adults and children with primary pulmonary hypertension. In both groups there was a close correlation between medial hypertrophy and the degree of vasoconstriction, suggesting that medial hypertrophy is the result of prolonged and intense increase in vasomotor tone in the muscular pulmonary arteries and that vasoconstriction is indeed the initial event in the pathogenesis of plexogenic arteriopathy.[3 7]

We did not confirm our previous observation of a difference in medial thickness between adults and children.[3] This may be because we excluded all arteries with secondary atrophy of the media, which was more severe in adults. Adults, however, had significantly higher scores for the index of pulmonary vascular disease, not attributable to the numbers of plexiform lesions. These were generally numerous but their numbers per square centimetre were not significantly different in the two age groups. The higher scores in adults were the result of increased severity of intimal fibrosis, which often extended over a lengthy course within the arteries and was therefore seen in multiple arterial cross sections. In an individual patient the index of pulmonary vascular disease depends not only on the degree of concentric laminar intimal fibrosis but also on the degree of intimal fibrosis developing as a result of the organisation of thrombi or thromboemboli or with advancing age. It is very unlikely that the observed difference between adults and children was the result of changes with age, which are almost always slight and tend to develop above the age of 40 years; few of our patients were as old as this. Eccentric patchy intimal fibrosis due to organised thrombi or emboli was seen in only nine adults and in one child and these lesions were numerous in only five cases. There is, therefore, no doubt that concentric laminar intimal fibrosis was far more advanced in our adult patients than in children, just as in children this type of intimal fibrosis increases with age.[3] Also, when patients with thrombotic lesions were excluded, the difference in the index of pulmonary vascular disease between adults and children was still statistically significant.

It is likely that severe and prolonged vasoconstriction initiates intimal lesions, possibly by damaging the endothelium. There is also evidence that spastic constriction may induce fibrin imbibition and necrosis of the arterial wall, which in turn may promote the development of plexiform lesions.[8] In this context, correlation between medial hypertrophy and index of pulmonary vascular disease in adult patients is important. This correlation appears to be absent in children, despite the fact that severity of medial hypertrophy and numbers of plexiform lesions are similar in adults and children. The absence of a clear correlation between degree of vasoconstriction and index of pulmonary vascular disease suggests that there may be less active contraction of arterial smooth muscle in advanced hypertensive pulmonary vascular disease.

Since adults and older children in whom primary pulmonary hypertension develops have a thin media before the onset of the disease, it is possible that medial hypertrophy evolves more gradually in adults than in young children and that because the clinical course is longer in adults they may be at increased risk of developing intimal lesions. Severe episodes of vasoconstriction frequently cause fibrinoid necrosis of the arterial wall and subsequent development of plexiform lesions when medial hypertrophy is not severe. It is possible that adequate medial hypertrophy gives some protection against the development of plexiform lesions whereas fibrinoid necrosis is more likely to occur when intense vasoconstriction occurs in vessels with lesser degrees of medial hypertrophy.[9]

We conclude that severe intimal lesions do not always precede the development of fibrinoid necrosis and plexiform lesions. Particularly in children, fibrinoid necrosis and plexiform lesions may appear in patients who until that point have reversible pulmonary vascular disease. On the other hand, by the time that plexiform lesions are seen in adults severe and irreversible intimal fibrosis is usually present.

Our findings have practical implications for vaso-

dilator treatment. Vasodilators including hydralazine and diazoxide have been used in the treatment of primary pulmonary hypertension with varying success.[10-12] Also, spontaneous regression has been reported in patients with primary pulmonary hypertension.[13 14]

The results of our study indicate that should the search for more efficient pulmonary vasodilator drugs be successful, children are particularly likely to benefit. It is probable that in children the arterial changes will be reversible until plexiform lesions appear. In such patients the histological picture will probably be one of medial hypertrophy alone or in combination with reversible cellular intimal proliferation; even if there is concentric laminar intimal fibrosis it is likely to be mild. In adults even before plexiform lesions are present intimal fibrosis will be so severe that no regression can be expected with vasodilator treatment.

## References


1 Yamaki S, Tezuka F. Quantitative analysis of pulmonary vascular disease in complete transposition of the great arteries. *Circulation* 1976; **54:** 805–9.

2 Yamaki S, Horiuchi T, Ishizawa E, Mohri H, Fukuda M, Tezuka M. Indication for total correction of complete transposition of the great arteries with pulmonary hypertension. *J Thorac Cardiovasc Surg* 1980; **79:** 890–5.

3 Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation* 1970; **42:** 1163–84.

4 Walcott G, Burchell HB, Brown AL Jr. Primary pulmonary hypertension. *Am J Med* 1970; **49:** 70–9.

5 Evans W, Short DS, Bedford DE. Solitary pulmonary hypertension. *Br Heart J* 1957; **19:** 93–116.

6 Dingemans KP, Wagenvoort CA. Ultrastructural study of contraction of pulmonary vascular smooth muscle cells. *Lab Invest* 1976; **35:** 205–12.

7 Wood P. *Diseases of the heart and circulation.* 2nd ed. London: Eyre and Spottiswoode, 1960.

8 Wagenvoort CA, Wagenvoort N. Pulmonary vascular bed. Normal anatomy and response to disease. In: Moser KM, ed. *Pulmonary vascular diseases.* New York: Marcel Dekker, 1979: 1–109.

9 Yamaki S, Wagenvoort CA. Plexogenic pulmonary arteriopathy. Significance of medial thickness with respect to advanced pulmonary vascular lesions. *Am J Pathol* 1981; **105:** 70–5.

10 Rubin LJ, Peter RH. Oral hydralazine therapy for primary pulmonary hypertension. *N Engl J Med* 1980; **302:** 69–73.

11 Daoud FS, Reeves JT, Kelly DB. Isoproterenol as a potential pulmonary vasodilator in primary pulmonary hypertension. *Am J Cardiol* 1978; **42:** 817–22.

12 Honey M, Cotter L, Davies N, Denison D. Clinical and haemodynamic effects of diazoxide in primary pulmonary hypertension. *Thorax* 1980; **35:** 269–76.

13 Bourdillon PDV, Oakley CM. Regression of primary pulmonary hypertension. *Br Heart J* 1974; **38:** 264–70.

14 Fujii A, Rabinovitch M, Matthews EC. A case of spontaneous resolution of idiopathic pulmonary hypertension. *Br Heart J* 1981; **46:** 574–7.